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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,078	01/08/2004	David H. Reifsnyder	12441.00050/16331.004	6550

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Chiron Corporation
Intellectual Property
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
CARLSON, KAREN C	
ART UNIT	PAPER NUMBER
1656	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/753,078	REIFSNYDER ET AL.	
	Examiner	Art Unit	
	Karen Cochrane Carlson	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *20-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office Action is in response to the papers filed April 6, 2009.

Claims 1-57 are pending. Claims 20-49 are withdrawn. Thus, claims 1-19 and 50-57 are pending and under examination.

Benefit of priority is to August 13, 2003.

Withdrawn Rejections:

The previous rejections under 103 are withdrawn in favor of the rejections set forth below.

New Rejections:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-18, 50-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Diaz-Collier et al. (1993; EP 0 559 632).

Diaz-Collier et al. teach that a ala-TFPI preparation refolded and purified by the method disclosed in Example 1 (page 6+ and esp page 6, para. 2 regarding Ala-TFPI). This TFPI preparation was greater than 95% homogeneous (page 12, line 2), suggesting that there was less than 5% misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts of the TFPI. There is also no evidence or

indication that the preparation contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated.

While 10-18 and 56 are drawn to large scale pharmaceutical preparations of TFPI, these claims are included in this rejection because the pharmaceutical carrier is not designated.

Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims.

There is sufficient evidence that the product disclosed by the reference is Applicants' product, and the burden is shifted to Applicants to distinguish the two. See *In re Best*, 195 USPQ 430 and *Ex Parte Gray* 10 USPQ 2d 1922, 1923.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 10-19, 56, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diaz-Collier et al. (1993; EP 0 559 632) in view of Chen et al. (February 25, 2003, priority to 1999; U.S. 6,525,102).

Diaz-Collier et al. teach ala-TFPI preparations refolded and purified by the method disclosed in Example 1 (page 6+ and esp. page 6, para. 2 regarding Ala-TFPI). This TFPI preparation was greater than 95% homogeneous (page 12, line 2), suggesting that there was less than 5% misfolding, aggregation, carbamylation,

oxidation, deamidation, or cysteine adducts of the TFPI. There is also no evidence or indication that the preparation contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated.

Diaz Collier et al. do not teach that the pharmaceutical compositions comprising 20mM sodium citrate, 300 mM L-arginine, and 5 mM methionine, pH 5.5. However, at page 3, para. 2, Diaz-Collier et al. teach that an advantage of their inventions is that the TFPI has substantially greater homogenicity than TFPI obtained in mammalian SK hepatoma cells and list 3 advantages of TFPI produced in E. coli (page 3, paras, 3, 4, and 5): A) no phosphorylation of TFPI, B) less proteolytic internal cleavages, and C) no glycosylation of TFPI.

Chen et al. teach a preparation comprising TFPI in 10mM sodium citrate and 300 mM arginine buffer at pH 5.5 (Col. 3, lines 41-45; Example 8). At Col. 10, lines 21+, Chen et al. teach to stabilize the pharmaceutical composition with methionine to protect TFPI from oxidation. Chen et al. teach that the addition of arginine to a TFPI preparation protects TFPI from aggregation (Col. 6, lines 8-55).

Therefore, it would have been obvious to one of ordinary skill in the art make pharmaceutical compositions comprising sodium citrate, L-arginine, and methionine and the TFPI produced by Diaz-Collier et al. because Diaz-Collier et al. teach that their preparation of TFPI is 95% homogeneous and is not phosphorylated or glycosylated over the prior art preparations of TFPI and Chen et al. teach that pharmaceutical compositions of TFPI comprising sodium citrate, L-arginine, and methionine are useful to administer TFPI in a clinical setting.

Applicants argue at page 15 of their response that Diaz-Collier et al. do not teach commercial-scale preparations and pharmaceutical formulations comprising TFPI and TFPI analogs that meet FDA standards of purity in Phase III clinical trials (that is, less than 12% modified species). In response, Diaz-Collier et al. state that their preparation of TFPI is at least 95% homogeneous; therefore, one can only conclude that there are less than 5% modified species in the preparation taught by Diaz-Collier et al.

Applicants urge (page 15-17) that the two important features of the claimed preparations are commercial-grade purity of less than 12% modified species, and commercial scale quantity of greater than 200g. The issue of 12% modified species has been addressed above. Regarding that the quantity be greater than 200 g is simply a matter of collecting additional TFPI fractions. The limitation that the preparation have at least 200g of TFPI or analogues thereof carries no patentable weight because the amount of TFPI does not change the biochemical characteristics of TFPI. For example, if one takes a teaspoon of sugar from a sugar jar, the sugar is not materially changed. This analogy applies to the instant claims. It is noted that no concentration of TFPI is provided, though this a concentration of TFPI would not negate this rejection.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson whose telephone number is 571-272-0946. The examiner can normally be reached on 6:00 AM - 4:00 PM, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Karen Cochrane Carlson, Ph.D./

Primary Examiner, Art Unit 1656